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APPLICATION NO. 09/275,924	FILING DATE 08/17/99	FIRST NAMED INVENTOR GALLO	ATTORNEY DOCKET NO. ABGX-2-CIP
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HM12/0216

EXAMINER DIBRINO, M

ART UNIT 1644	PAPER NUMBER 4
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DATE MAILED: 02/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/375,924

Applicant

Gallo et al

Examiner
Marianne DiBrino

Group Art Unit
1644



- ☐ Responsive to communication(s) filed on _____
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle* 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

- ☒ Claim(s) 1-11 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1-11 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☒ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Claims 1-11 are pending and are being acted upon presently.
2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. There is no CRF, no paper copy of the sequence listing for sequences such as SEQ ID NOS: 1, 2, 3 and 4 appearing on page 42; also, applicants are required to submit a statement that the content of the paper and computer readable are the same and where applicable, include no new matter.
3. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification. For example, SEQ ID numbers are required in the Brief Description of the Drawings for the sequences appearing in Figure 2.
4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the declaration is required to cite priority to the provisional application under 35 U.S.C. 119(e).
5. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
6. Claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
7. Claims 1-11 are indefinite in the recitation of "FcRn binding " because it is not clear what this term encompasses.
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the

applicant for a patent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103^o and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-4, 6, 7, 9 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Junghans (WO 97/43316).

Junghans teaches that the FcRp and the FcRn are the same receptor (especially page 2, lines 16-21). Junghans teaches a method for producing an antibody which has an extended half-life in the circulatory system of a subject comprising modifying the structure of an antibody by recombinant means which has a first FcRn binding domain (especially claims 19, 23, 26, 27 and Table 1). "VLHQ" (especially first four amino acid residues of SEQ ID NO: 9, 5th line of Table 1 in column 3) and "HNHY" (especially last line of column 3 in Table 1) are two exogenous FcRn binding domains (especially lines 30-36 on page 7 and line 1 on page 8). Junghans teaches a modified antibody which has an extended half-life in a subject (including mammals) comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody (especially claims 1, 5, 6, 10 and Table 1). Junghans also teaches an IgA molecule (IgA is a dimer) which is altered recombinantly to possess three FcRn binding domains "KTLMISRTP" (the second line of column 3 in Table II, SEQ ID NO: 12 exclusive of amino acid residue number 1), "VLHQ" (the fifth line of column 3 in Table II, amino acid residues 1-4 of SEQ ID NO: 9) and "HNHY" (the last line of column 3 in Table II, SEQ ID NO: 9). Junghans further teaches an antibody or antigen-binding fragment of an antibody produced against the FcRp which is included as a modification to another molecule (especially page 3, lines 23-25). Junghans teaches that this other molecule can be an immunoglobulin (especially page 4, lines 7-13).

The reference teachings anticipate the claimed invention.

11. Claims 1-11 are under 35 U.S.C. § 103(a) as being unpatentable over Junghans (WO 97/43316) in view of Doerschuk et al (U.S. Patent No. 5,702,946), Ladner et al (U.S. Patent No. 4,946,778), Junghans (Immunologic Research, 1997, Vol. 16, pages 29-57) and Braxton (U.S. Patent No. 5,766,897).

Junghans teaches that the FcRp and the FcRn are the same receptor (especially page 2, lines 16-21). Junghans teaches a method for producing an antibody which has an extended half-life in the circulatory system of a subject comprising modifying the structure of an antibody by recombinant means which has a first FcRn binding domain (especially claims 19, 23, 26, 27 and Table 1). "VLHQ" (especially first four amino acid residues of SEQ ID NO: 9, 5th line of Table 1 in column 3) and "HNHY" (especially last line of column 3 in Table 1) are two exogenous FcRn binding domains (especially lines 30-36 on page 7 and line 1 on page 8). Junghans teaches a modified antibody which has an extended half-life in a subject (including mammals) comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody (especially claims 1, 5, 6, 10 and Table 1). Junghans also teaches an IgA molecule (IgA is a dimer) which is altered recombinantly to possess three FcRn binding domains "KTLMISRTP" (the second line of column 3 in Table II, SEQ ID NO: 12 exclusive of amino acid residue number 1), "VLHQ" (the fifth line of column 3 in Table II, amino acid residues 1-4 of SEQ ID NO: 9) and "HNHY" (the last line of column 3 in Table II, SEQ ID NO: 9). Junghans further teaches an antibody or antigen-binding fragment of an antibody produced against the FcRp which is included as a modification to another molecule (especially page 3, lines 23-25). Junghans teaches that this other molecule can be an immunoglobulin (especially page 4, lines 7-13).

Junghans does not teach said antibody binds specifically to IL-8, nor is a single chain antibody.

Doerschuk et al discloses anti-IL-8 monoclonal antibodies and their use in treatment of inflammatory disorders (especially Abstract).

Ladner et al discloses the advantages of single chain antibodies over conventional are smaller size, greater stability and significantly reduced cost (especially column 3, lines 33-35).

Junghans (Imm. Res.) teaches that at low serum IgG concentrations the FcRn receptor binds all endocytosed IgG and efficiently returns the IgG to circulation, yielding a long IgG survival, but at high IgG concentrations, the receptor is saturated by IgG and the major fraction of the IgG is unbound by the receptor and passes to catabolism, yielding a more rapid net catabolism and abbreviated survival (especially page 34, last paragraph of column 1 and continuing on to column 2).

Braxton discloses the development of protein therapies is hampered by the relatively short half-life of proteins after administration (especially column 1, lines 47-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the teachings of Junghans of a modified antibody comprising at least a first and second FcRn binding domain a ways of producing said antibody recombinantly, the teaching of Doerschuk et al of anti-IL-8 monoclonal antibodies, including their use in treatment of inflammatory disorders, the advantages of single chain antibodies over conventional as taught by Ladner, the teaching of Junghans of the saturation of FcRn at high serum IgG concentrations and the disclosure of Braxton of the need for increasing the short half-life of therapeutic proteins after administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to modify the anti-IL-8 antibody of Doerschuk et al to comprise at least a first and second FcRn binding domain in order to increase the half-life in circulation as taught by Junghans, especially given the disclosure of Doerschuk et al of the therapeutic usefulness of anti-IL-8 antibodies in inflammatory disorders, the teaching of Kallos et al of a direct relationship between serum IgG concentration and its catabolic rate and the disclosure Braxton of the desirability of increasing the half life of therapeutically administered proteins. One of ordinary skill in the art at the time the invention was made would have been motivated to produce said anti-IL-8 monoclonal antibody as a single chain antibody, especially given the disclosure of Ladner et al of the advantages of single chain antibodies over conventional antibodies, and in particular, their greater stability.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because it was well known in the art that FcRn binding domains were responsible for increased half-life of IgG antibodies, that FcRn binding by IgG was saturable, anti-IL-8 monoclonal antibodies and their therapeutic usefulness were well known and the advantages of single chain antibodies were well known in the art as well. In addition, the need for increasing the half-life of therapeutically administered proteins was well known in the art and the direct relationship between serum IgG concentration and catabolic rate was well known in the art. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 1-11 are under 35 U.S.C. § 103(a) as being unpatentable over Presta et al (WO 96/32478) in view of Doerschuk et al (U.S. Patent No. 5,702,946), Ladner et al (U.S. Patent No. 4,946,778), Kallos et al (Progr. Allergy, Vol. 13, 1969, pages 1-109) and Braxton (U.S. Patent No. 5,766,897).

Presta et al teaches proteins that are modified to contain one or more "salvage receptor binding epitope", i.e., FcRn binding domains, of the Fc region of an IgG molecule that is responsible for increasing the in vivo serum half-life of the IgG molecule (especially page 5, lines 19-22,

page 2, lines 15-38, page 3, lines 1-14 and claims). Presta et al teaches a method of modifying the half-life of said proteins comprising recombinantly linking more than one FcRn binding domain (see entire document).

Presta et al does not teach said proteins are full length antibodies, including full length single chain antibodies, nor does he teach said proteins are anti-IL-8 antibodies.

Doerschuk et al discloses anti-IL-8 monoclonal antibodies and their use in treatment of inflammatory disorders (especially Abstract).

Ladner et al discloses the advantages of single chain antibodies over conventional are smaller size, greater stability and significantly reduced cost (especially column 3, lines 33-35).

Kallos et al teach a direct relationship between the serum IgG concentration and its fractional catabolic rate in man and some animals (especially page 91, column 2, lines 1-3).

Braxton discloses the development of protein therapies is hampered by the relatively short half-life of proteins after administration (especially column 1, lines 47-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the teachings of Presta et al of proteins with increased-half lives comprising recombinantly engineered proteins with salvage receptor binding domains, the teaching of Doerschuk et al of anti-IL-8 monoclonal antibodies, including their use in treatment of inflammatory disorders, the advantages of single chain antibodies over conventional as taught by Ladner et al, the teaching of Kallos et al of a direct relationship between serum IgG concentration and its catabolic rate and the disclosure of Braxton of the relatively short half life of proteins administered therapeutically.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the full-length anti-IL-8 monoclonal antibody of Doerschuk et al as the protein in the invention of Presta et al in order to increase the half-life in circulation, especially given the teaching of Doerschuk et al of the therapeutic usefulness of anti-IL-8 antibodies in inflammatory disorders, the teaching of Kallos et al of a direct relationship of serum IgG concentration and catabolic rate and the disclosure of Braxton of the desirability of increasing the serum half life of therapeutically administered proteins. One of ordinary skill in the art at the time the invention was made would have been motivated to produce said anti-IL-8 monoclonal antibody as a single chain antibody, especially given the teaching of Ladner et al of the advantages of single chain antibodies over conventional antibodies, and in particular, their greater stability.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because it was well known in the art that FcRn binding domains were responsible for increased half-life of IgG antibodies, anti-IL-8 monoclonal antibodies and their therapeutic usefulness were well known and the advantages of single chain antibodies were well known in the art as well. In addition, the need for increasing the half-life of therapeutically administered proteins was well known in the art and the direct relationship between serum IgG concentration and catabolic rate was well known in the art. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 1-11 are under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al (WO 94/04689) in view of Doerschuk et al (U.S. Patent No. 5,702,946), Ladner et al (U.S. Patent No. 4,946,778), Kallos et al (Progr. Allergy, Vol. 13, 1969, pages 1-109) and Braxton (U.S. Patent No. 5,766,897).

Pastan et al teach fusion proteins comprising toxins and the Fc region of IgG, preferably CH2, in order to increase serum half life and methods of making the fusion proteins (especially Abstract, page 12, lines 11-17, page 3, lines 35-38, page 4, lines 1-3 and claims).

Pastan et al does not teach said proteins are full length antibodies, including full length single chain antibodies, nor does he teach said proteins are anti-IL-8 antibodies.

Doerschuk et al discloses anti-IL-8 monoclonal antibodies and their use in treatment of inflammatory disorders (especially Abstract).

Ladner et al discloses the advantages of single chain antibodies over conventional are smaller size, greater stability and significantly reduced cost (especially column 3, lines 33-35).

Kallos et al teach a direct relationship between the serum IgG concentration and its fractional catabolic rate in man and some animals (especially page 91, column 2, lines 1-3).

Braxton discloses the development of protein therapies is hampered by the relatively short half-life of proteins after administration (especially column 1, lines 47-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the teachings of Pastan et al of proteins with increased-half lives comprising the Fc domain, including the CH2 region, the teaching of Doerschuk et al of anti-IL-8 monoclonal antibodies, including their use in treatment of inflammatory disorders, the advantages of single chain antibodies over conventional as taught by Ladner et al, the teaching of Kallos et al of a direct relationship between serum IgG concentration and its catabolic rate and the disclosure of Braxton of the

relatively short half life of proteins administered therapeutically.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the full-length anti-IL-8 monoclonal antibody of Doerschuk et al as the protein in the invention of Pastan et al in order to increase the half-life in circulation, especially given the teaching of Doerschuk et al of the therapeutic usefulness of anti-IL-8 antibodies in inflammatory disorders, the teaching of Kallos et al of a direct relationship of serum IgG concentration and catabolic rate and the disclosure of Braxton of the desirability of increasing the serum half life of therapeutically administered proteins. One of ordinary skill in the art at the time the invention was made would have been motivated to produce said anti-IL-8 monoclonal antibody as a single chain antibody, especially given the teaching of Ladner et al of the advantages of single chain antibodies over conventional antibodies, and in particular, their greater stability. Instant claims 1-11 are included because FcRn binding domains are present within the Fc region, particularly the CH2 region, of IgG.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because it was well known in the art that FcRn binding domains were responsible for increased half-life of IgG antibodies, anti-IL-8 monoclonal antibodies and their therapeutic usefulness were well known and the advantages of single chain antibodies were well known in the art as well. In addition, the need for increasing the half-life of therapeutically administered proteins was well known in the art and the direct relationship between serum IgG concentration and catabolic rate was well known in the art. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

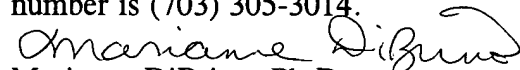
15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

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Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.


Marianne DiBrino, Ph.D.

Patent Examiner

Group 1640/Technology Center 1600

February 14, 2000



RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP 1600 *1600*

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Serial No
09/375-924

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
- ☐ 7.

Other: _____

Applicant must provide:

- ☒ An initial ~~or substitute~~ computer readable form (CRF) copy of the "Sequence Listing"
- ☒ An initial ~~or substitute~~ paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.